RESPONSE UNDER 37 C.F.R. 1.116
EXPEDITED PROCEDURE
EXAMINING GROUP 1648

Attorney Docket No. 9013-31 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Welch et al.
Serial No.: 09/889,645
Filed: January 24, 2002
For: TREATING PROTEIN-CONTAINING LIQUIDS

Confirmation No. 8639
Group Art Unit: 1648
Examiner: Agnieszka Boesen

Date: June 22, 2009

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REASONS FOR PRE-APPEAL BRIEF REQUEST FOR REVIEW

Sir/Madam:

This document is submitted in support of the Pre-Appeal Brief Request for Review filed concurrently with a Notice of Appeal for the above-referenced patent application. Applicants hereby request a Pre-Appeal Brief Review (hereinafter, "Request") for the claims rejected in the final Office Action dated December 23, 2008 (hereinafter, "Final Action"). This Request is provided herewith in accordance with the rules set forth in the Official Gazette of July 12, 2005. No amendments are being filed with this Request.

It is not believed that any fee(s), including fees for additional claims, are required, beyond those that may otherwise be provided for in documents accompanying this submission. In the event, however, that any requests, petitions or extensions of time for the accompanying response are required to prevent abandonment of this application, Applicants submit that such an extension is also hereby petitioned for under 37 C.F.R. §1.136(a) and/or a request be granted pursuant to 37 C.F.R. §1.114. Any additional fees believed to be due in connection with this submission may be charged to our Deposit Account No. 50-0220, or any overpayment may be credited to the same.

USPTO Customer No. 20792
Myers Bigel Sibley & Sajovec
Post Office Box 37428
Raleigh, North Carolina 27627
Telephone: 919/854-1400
Facsimile: 919/854-1401

CERTIFICATION OF TRANSMISSION

I hereby certify that this correspondence is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4) to the U.S. Patent and Trademark Office on June 22, 2009.

Betty Lou Rosser

REMARKS

Applicants hereby request a Pre-Appeal Brief Review (hereinafter "Request") of finally rejected pending claims 1, 3, 6-10, 12-16, 25, 28 and 31-37. This Request notes the clear error in facts and/or the lack of elements required for a *prima facie* rejection of the pending claims responsive to the Final Action.

In the Final Action, the pending claims stand rejected under 35 U.S.C. §103(a) as being unpatentable over GB 2 045 828 A to Ostreicher et al. (hereinafter, "Ostreicher et al.") in view of WO 96/05846 to Nebe (hereinafter, "Nebe") as evidenced by Encyclopedia Britannica. *See* Final Action, page 2.

I. The Present Invention

The present invention is directed generally to a method of removal of abnormal infective prion proteins associated with transmissible spongiform encephalopies (TSEs) from an aqueous liquid. More specifically, the present invention addresses the problem of removing soluble prion protein contaminants from solutions of soluble blood plasma proteins such as immunoglobublins and albumin. Such solutions are clear solutions.

Prion proteins are soluble proteins, i.e., not particles, much like blood plasma proteins that are soluble proteins. It is well understood that proteins in plasma are soluble (by definition) and may be aggregated in solution without forming particulates (e.g. von Willebrand factor). At the time of the present invention, the nature of prion proteins was poorly understood as described in Applicants' response to the final Office Action dated February 24, 2004. Accordingly, one of ordinary skill in the art would not be well informed, if at all, regarding how to remove one type of soluble protein, e.g., prions, from a solution including other soluble proteins, e.g., blood plasma proteins.

The present inventors have made the surprising discovery that a depth filter formed of a matrix comprising (a) a binder and (b) kieselguhr or perlite particles or mixtures thereof and having a pore size providing a retention less than 6 μm is able to pass soluble blood plasma proteins of pharmaceutical interest, **but is also capable of retaining the undesirable prion proteins**– as noted previously, a soluble protein. It is surprising that a depth filter having this wide pore size is able to remove prion proteins where one of ordinary skill in the art would have expected that the prion proteins would have passed through a filter of such wide pore size.

II. The Cited References

Ostreicher et al.

As noted in previous responses, Ostreicher et al. describes a conventional depth filter including kieselguhr/perlite employed to remove particles, including submicron particles, bacteria, etc., from various liquids. It is known that these conventional depth filters are used to filter solutions where soluble proteins are known to pass through the filter and particulates are retained on the filter. Since soluble plasma proteins pass through the filter, the artisan of ordinary skill would have no reason to believe that prions, i.e., soluble proteins, would be captured by a filter having this greater width.

Nebe

Nebe describes the partial removal of prions using a succession of nylon pre-filters of size 2 µm, 0.8 µm and 0.2 µm (A discussion of pore size is presented in greater detail in Applicants' response to the non-final Office Action dated August 24, 2007). However, this series of filtrations does not remove the prions to the extent that the liquid is non-infective where there are at least $10^{4.97}$ units remaining. Several additional ultrafiltration steps are required before the prions are removed to the point of rendering the liquid non-infective. From Nebe, one of ordinary skill in the art learns that ultrafiltration using membranes which retain much smaller molecules than even the 0.2µm pre-filter is required to remove the prion proteins to render the liquid non-infective. However, one of ordinary skill in the art would also know that such ultrafiltration membranes retain **all** the soluble plasma proteins of pharmaceutical interest.

It is important to note that ultrafiltration membranes are usually described and sold in terms of their molecular weight cutoff (not by pore size). Accordingly, the cutoff of the American S1Y30 ultrafilter of Nebe is approximately 30,000 molecular weight. An ultrafilter membrane having a 30,000 molecular weight (also expressed as 30 kDa) cutoff will not pass any proteins larger than this size, which includes all plasma proteins of interest– thrombin (36 kDa), coagulation factors and albumin (50 to 70 kDa), immunoglobulins (180 kDa) and von Willebrand factor (>1000 kDa), but which also includes abnormal prion protein (>33 to 35 kDa).

Thus, while Nebe uses an ultrafiltration to retain prion protein and separate prion protein from smaller cellular debris, Nebe would not use ultrafiltration to separate prion protein from similar or larger protein. While Ostreicher et al. can use depth filters to separate sub-micron **particulates** from biological **solutions**, neither method alone or in combination would teach that

these similar species of prion protein and plasma protein could be separated from each other.

Instead, the combination of these cited references results in the following implausible scenario: First, the blood plasma protein solution is filtered using a depth filter of kieselguhr/perlite as discussed in Ostreicher et al. Then, the blood plasma protein solution is subjected to the pre-filtration stages of Nebe followed by ultrafiltration using the ultrafiltration membrane with a molecular weight cut-off of 30,000 kDa. Nebe teaches that the pre-filtration steps and the ultrafiltration step are both **required** in order to obtain a liquid filtrate that is non-infective. However, it is well known that soluble blood plasma proteins are retained by an ultrafiltration membrane. Therefore, when the blood plasma protein solution is filtered using the Nebe filtration steps, neither prion protein nor plasma protein of interest would pass through the filter into the filtrate. Thus, the combination of Ostreicher et al. and Nebe would not only remove the prion proteins, but all the soluble blood proteins would be removed and **no soluble proteins would remain in the liquid filtrate**. This would not address the problem to be solved by the present invention, namely to render plasma proteins of pharmaceutical interest safe by removal of pathogenic prion protein. In contrast, the present invention provides a method that removes the prion proteins from the liquid leaving a non-infective liquid that includes the desired blood plasma proteins.

III. The Final Office Action

On page 3 of the Final Action, the Examiner asserts, "One would have had a reasonable expectation of success to filter human plasma through Ostreicher's filter because Ostreicher teaches using his filter to filter biological liquids and because Ostreicher's filter removes submicron contaminates." Applicants respectfully submit that this reference discusses removal of submicron particulates of the type discussed on page 10, line 47-64 of the reference; namely, impurities, e.g., bacteria, viruses or pyrogens, and retention of submicronic particles, removal of bacterial contaminants and resolution of colloidal hazes– All of which are particulates or have a particulate-like character. There is no teaching or suggestion of the retention of soluble proteins or that such filters may retain soluble prion proteins. Prion proteins are not "submicron contaminates" nor are they similar to submicron contaminants.

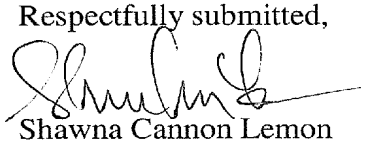
On page 3 of the Final Action it is further asserted that "Nebe teaches that prion proteins can be removed using filters that provide retention from 2.0-0.2 microns." However, this is a mischaracterization. Nebe indicates that the level of prion protein can be reduced using the

referenced pre-filters; however, these pre-filters do not eliminate prion infectivity, and any residual prion infectivity would be dangerous in a human pharmaceutical preparation where infectivity would be passed to the patient. The partial prion removal is believed to be due to the removal of cellular debris, which is associated with some of the prion protein burden when solid tissues (e.g. thymus glands) are the starting material. According to Nebe, **elimination of prion infectivity is only accomplished when multiple ultrafiltration stages are employed**. However, as noted above, the ultrafiltration membrane would also retain soluble blood plasma proteins from which the prion proteins are intended to be separated.

Lastly, on page 4 of the Final Action, the Examiner asserts that "[i]t is the position of the Office that prion present in human plasma would be expected to be removed from plasma using Ostreicher's filter because Ostreicher's filter provides retention less than 6 μm and because Nebe teaches that prion proteins can be removed using filters that provide retention from 2.0-0.2 μm." First, Ostreicher nowhere indicates that the filters employed provide a retention of less than 6 μm. Second, Nebe does not teach that prion proteins can be removed completely using filters that provide retention from 2.0-0.2 μm. As noted above, the Nebe pre-filters having a retention of 2.0-0.2 μm only partially removing prions leaving an infectious, nonsterile material that is wholly unsuitable for use as a human pharmaceutical or a veterinary medicine. Additional steps and multiple filtrations are required to remove the prion proteins; and when combined with Ostreicher, the desired blood plasma proteins would also be removed. Thus, the combination of Ostreicher and Nebe fails to teach or suggest the recited method of removing abnormal infective prion proteins associated with TSEs from an aqueous liquid and this combination fails to provide one of ordinary skill in the art any reasonable expectation of success of obtaining a liquid that **excludes** the prion proteins and **includes** the blood plasma products.

For at least the foregoing reasons, Applicants respectfully request that the present application be reviewed and that the rejection of claims 1, 3, 6-10, 12-16, 25, 28 and 31-37 be reversed by the appeal conference prior to the filing of an appeal brief. Moreover, the Examiner is encouraged to telephone the undersigned at 919-854-1400 for resolution of any outstanding issues.

Respectfully submitted,



Shawna Cannon Lemon
Registration No. 53,888